PROGNOSTIC SIGNIFICANCE OF MORPHOLOGICAL AND CYTOCHEMICAL MARKERS IN ADULT ACUTE MYELOGENOUS LEUKAEMIA: CONCEPTS AND OBSERVATIONS

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INTRODUCTION

PRESENT trends of different therapeutic regimens for various acute leukaemias necessitates an accurate definition of the type of blastic proliferation, (Hayhoe *et al.* 1964; Tan *et al.* 1977). Using classic morphological criteria (Bennet *et al.* 1968; Galton and Dacie 1975) cases of adult myelogenous leukaemia were analysed with standard cytochemical markers. These morphological patterns were then related to survival times. Several authors have investigated these relationship with responses to treatment and survival rates. Anner *et al.* (1977) have shown that the subclassification of granulocytic leukaemia according to the presence or absence of Auer rods and percentages of peroxidase positive blasts fail to show significant differences in survival time.

MATERIAL AND METHOD

All the nine patients studied were referred to the General Hospital, Kuala Lumpur, University Kebangsaan division between September 1977 and May 1979 with the presumptive diagnosis of acute leukaemia and had received no prior treatment.

Venous blood was collected in EDTA and analysed on the Coulter S. Prepared smears were stained by Wright's stain and classification of leukaemic blast cell type was performed according to the classic morphologic criteria, (Galton and Dacie 1975; Bennet *et al.* 1968). The cyctochemical stains employed are peroxidase, periodic acid schiff (PAS) reaction, and a non specific esterase stain utilising the substrate Naphthol- AS-D Acetate (NASDA) with and without sodium fluoride as an enzyme inhibitor (NASDA-F). The esterase of monocytes being completely inhibited by NaF in contrast to granulocytes and lymphocytes. All slides were checked for the presence of Auer rods. Examination of bone marrow specimens were obtained by aspiration from the posterior iliac crest or from the sternum, stained by May Grunwald Giemsa, and with standard cytochemical stains. The slides were assessed by two haematologists independantly.

TREATMENT PROTOCOL

This consisted of daily cytosine arabinoside 100mg/M^2 intravenously with either thioguanine 100mg/M^2 orally or with daunorubicin 1.5mg/kg intravenously on day 1 of each five day treatment schedules.

RESULTS

Nine cases of acute myelogenous leukaemia were diagnosed and their results are summarised in Table I. Their ages ranged from 13 to 42 years: consisting of four males and five female patients. They were further subclassified into four acute myelomonocytic and five myeloblastic leukaemias. No pure acute monocytic leukaemias were included in the study.

The patients with myeloblastic leukaemia with the lowest survival time had a haemoglobin below

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5gm/dl; total white cell count greater than $50x10^{9/1}$ and with blasts ranging from 75-85%. The patient with least survival time in this group was Auer rod negative. In either groups patients with ages greater than 35 years had survival times of less than 33 days; the longest survival time being between patients of 20 to 35 years. Shorter survival times were also associated with patients who at onset had a temperature 101°F or greater.

TABLE I : Acute Myelogenous Leukaemia: Common characteristics seen in acute myelomonocytic and myeloblastic leukaemia

	Myelomonocytic	Myeloblastic
Age	13 - 42 years	12 - 40 years
Sex	3 males 1 female	1 male 4 females
Race	3 Malays 1 Chinese	3 Malays 2 Chinese
Hb	less than 10mg/dl range 3.8 - 10	less than 10gm/dl range 2.9 - 7
TWDC	greater than $15x10^{9/1}$ range $15.8\text{-}86x10^{9/1}$	50% greater than $15x10^{9/1}$ range $6.0\text{-}384x10^{9/1}$
Blasts	46 - 80%	50 - 85%
Plat.	less than $60x10^{9/1}$	less than $60x10^{9/1}$
Auer Rods	3 negative	1 negative
	1 positive	4 positive
Survival Time	10 - 46 days	33 - 237 days*

(*Two alive at time of writing of this study)

DISCUSSION

Survival rates for patients with acute myelogenous leukaemia have increased considerably in the last two decades with the introduction of better treatment protocols. Anner (1977) had a median survival of 45.4 weeks in the subgroup without Auer rods; our range being 10 to 33 days.

In our limited study of nine cases, patients with Auer rod negative leukaemia had shorter survival than those who were Auer rod positive. In hospitals in this region most acute leukaemic patients are managed in open medical wards and the nearest measure to protective environment nursing is single room units; air laminar flow and barrier nursing are not currently available to all acute leukaemic patients (Levine 1976).

Prophylactice antibiotic cover consists of broad spectrum antibiotics which included a semi-synthetic penicillin carbenicillin and gentamycin. Non absorbable antibiotics were not used in this protocol. Immunotherapy consists of Bacille Calmette Guerin vacine (BCG) given only to one patient in our series.

In studying prognostic factors in relation with response to chemotherapy in acute myelogenous leukaemia in adults the following should be considered at onset. Age, infection, temperature 101°F or greater, total white and blast cell count, presence or absence of Auer rods, percentage of peroxidase positive blast cells, haemoglobin level and platelet count.

Currently all new cases admitted to the medical unit, University Kebangsaan Malaysia are treated by the regime of Gale and Cline (1977).

The treatment protocol is summarised in Fig. I. Patients are started on allorpurinol 100mg four times daily. Induction therapy consists of cytosine arabinoside (Ara C) 100mg intravenously over 30 minutes, thioguanine $100mg/M^2$ orally every twelve hours for seven days and daunorubicin $60mg/M^2$ intravenously on cycle days five, six and seven. Consolidation therapy consisted of two cycles of Ara-C and thioguanine every twelve hours for five days, followed by a single injection of daunorubicin. Consolidation cycles were given at twenty one day intervals. Prophylactic central nervous system therapy consists of 2400 rads cranial irradiation and five doses of intrathecal Ara-C $100mg/M^2$ during the consolidation phase. The patients were then randomised to receive either monthly five day cycles of Ara C/thioguanine alternating with a single dose of daunorubicin. Immunotherapy consists of weekly injections of BCG.

No cell separator is available at our centre: buffy coats being transfused when available to neutropaenic patients.

Other supportive measures included packed

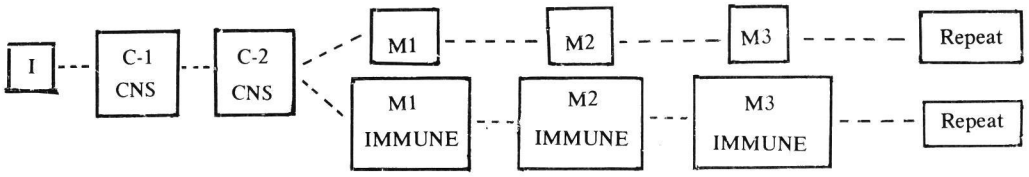

Fig. I - Acute Leukaemia Protocol of Gale and Cline consisting of an induction cycle consolidation and maintenance cycles, central nervous system prophylaxis and immunotherapy

I — induction cycle
C-1, C-2 — consolidation cycles
M-1, M-2, M-3 — maintenance cycles
CNS prophylaxis
immune — immunotherapy

red cell transfusions and platelet concentrates as necessary.

Cytogenetic, immunologic, cultural and cell kinetic studies have prognostic implications (Rowley 1978; Zueller 1977; Alimea 1977; Ross 1977) but these investigations are not within the reach of the average haematologist in this country. Comparative studies within this region are necessary in the wake of changing trends in the treatment of acute leukaemia using prognostic markers that include clinical appraisal, haemogram studies, morphological and cytochemical criteria available at most conventional laboratories.

SUMMARY

Nine adult patients with acute myelogenous leukaemia were studied for assessment of their morphological and cyctochemical characteristics in relation to survival rates with conventional antileukaemic therapy from September 1977 to May 1979. Correlation is limited by the small number of patients. Significant prognostic factors considered are age, temperature, total white cell count, total blast cell count, type of blast cell, presence or absence of Auer rods, haemoglobin and platelet count.

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